

REMARKS

Claims 28-42, 45, 47, 50, 53-54 and 57-74 are pending in this application.

Claims 1-27, 43, 44, 46, 48-49, 51-52 and 55-56 have previously been canceled without prejudice or disclaimer. Claims 28, 47, 50, 57, 59, 64, 65, 73 and 74 have been amended. Claims 28-42, 47-50, 52, 54, 57 and 58-59 have been rejected.

Claims 44-45, 48-49 and 52 are withdrawn from consideration as being directed to a non-elected species. Applicants note that upon allowance of a generic claim, Applicants will be entitled to consideration of claims to additional species which are written in dependent form or otherwise include all the limitations of an allowed generic claim as provided by 37 C.F.R. § 1.141.

Claims 1-27, 43-44, 46, 48-49, 51-52 and 55-56 have been canceled without prejudice or disclaimer, and claims 28, 47, 50, 57, 59, 64, 65, 73 and 74 have been amended, for the sole reason of advancing prosecution. Applicants, by cancelling or amending any claims herein, make no admission as to the validity of any rejection made by the Examiner against any of these claims. Applicants reserve the right to reassert any of the claims canceled herein or the original claim scope of any claim amended herein, in a continuing application.

Claims 28, 47, 50, 57, 59, 64, 73 and 74 have each been amended to replace the trademark term "Copaxone" with the generic description "glatiramer acetate." Please see the *Highlights of Prescribing Information* for COPAXONE filed herewith. No new matter has been added.

Claim 64 has been amended to recite, in part, "and the protein or polypeptide is not encapsulated in the one or more colloidal particles." Support for this amendment appears throughout the specification and claims as originally filed. No new matter has been added.

Claim 65 has been amended to be properly dependent on independent claim 64. No new matter has been added.

The specification has been amended at pages 4, 9, 10, 11 and 12 to capitalize the trademarked terms "COPAXONE" and "BIACORE." Also, a generic description of COPAXONE has been added, at page 4, 2nd full paragraph, to the specification. No new matter has been added.

In view of the remarks set forth below, further and favorable consideration is respectfully requested.

I. *At page 4 of the Official Action, claim 65 has been objected to for a minor informality.*

The Examiner asserts that claim 65 should properly be dependent on independent claim 64 and not claim 63.

Claim 65 has been amended to properly depend from independent claim 64. Accordingly, the Examiner is respectfully requested to withdraw this objection.

II. *At page 4 of the Official Action, claim 64 has been rejected under 35 USC § 112, first paragraph, as failing to comply with the written description requirement.*

The Examiner asserts that the specification and claims as originally filed do not support claim 64 in view of the lack of the limitation "and the protein or polypeptide is not encapsulated in the one or more colloidal particles."

In view of the following, this rejection is respectfully traversed.

Claim 64 has been amended to recite, in part, “and the protein or polypeptide is not encapsulated in the one or more colloidal particles.” Accordingly, the Examiner is respectfully requested to withdraw this rejection.

III. *At page 6 of the Official Action, claims 64-65 and 67-68 have been rejected under 35 USC § 102(b) as being anticipated by Allen et al.*

The Examiner asserts that Allen et al. teaches a pharmaceutical composition comprising a therapeutically effective amount of a protein and neutral colloidal particles. The protein can be a targeting antibody that is capable of externally binding the colloidal particle. The Examiner states that the reference further teaches liposome-entrapped compounds, such as peptide hormones, etc.

The test for anticipation is whether each and every element as set forth is found, either expressly or inherently described, in a single prior art reference. *Verdegaal Bros. v. Union Oil Co. of California*, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987); MPEP § 2131. The identical invention must be shown in as complete detail as is contained in the claim. *Richardson v. Suzuki Motor Co.*, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989); MPEP §2131. The elements must also be arranged as required by the claim. *In re Bond*, 15 USPQ2d 1566 (Fed. Cir. 1990).

In view of the remarks set forth herein, this rejection is respectfully traversed.

Claim 64 has been amended to recite, in part, “and the protein or polypeptide is not encapsulated in the one or more colloidal particles.” Claims 65, 67 and 68 are each directly or indirectly dependent on independent claim 64.

Claim 64 as amended requires that the protein or polypeptide is not encapsulated in the one or more colloidal particles. Allen et al. requires that the interleukins and CSF are liposome-entrapped. Allen et al. does not teach or suggest that the protein or polypeptide is not encapsulated in one or more colloidal particles, as presently claimed.

Accordingly, Allen et al. do not teach each and every element of claims 64, 65, 67 and 68 as required for anticipation under 35 USC § 102(b). Thus, the Examiner is respectfully requested to withdraw this rejection.

IV. At page 8 of the Official Action, claims 28-34, 36-42, 57, 59-60, 62-65, 67-68 and 73-74 have been rejected under 35 USC § 103(a) as being unpatentable over Baru M in view of Martin et al. and Ishikawa et al. and Igari et al.

The Examiner asserts that “it would have been obvious to one of ordinary skill in the art to combine the teachings of Baru and Martin, since Baru teaches a pharmaceutical composition for parenteral administration comprising a therapeutically effective amount of a protein or polypeptide and substantially neutral colloidal particles, and teaches that the term ‘proteins or polypeptides capable of externally binding said colloidal particles’ includes proteins and polypeptides which,...are coagulation factors such as...Factor V and Martin et al teach Interferon gamma, G-CSF...and various attempts have been developed to develop sustained-release preparation. Therefore it would have been obvious to one of ordinary skill in the art to use the liposomes of Baru to increase the half life of these compounds. One of ordinary skill in the art would have been motivated to combine the teachings, since the prior arts all teach therapeutic composition containing PEG-neutral liposome, and Baru reference teaches that when

the liposomes do not encapsulate the therapeutic compound (Factor VIII), the smaller sized liposomes can be used which have a longer half-life in vivo, because they are not removed by the RES....”

In view of the remarks set forth herein, this rejection is respectfully traversed.

To establish a *prima facie* case of obviousness, the PTO must satisfy three requirements. First, as the U.S. Supreme Court very recently held in *KSR International Co. v. Teleflex Inc. et al.*, 550 U.S. 398 (2007), “a court must ask whether the improvement is more than the predictable use of prior art elements according to their established functions. ...it [may] be necessary for a court to look to interrelated teachings of multiple patents; the effects of demands known to the design community or present in the marketplace; and the background knowledge possessed by a person having ordinary skill in the art, all in order to determine whether there was an apparent reason to combine the known elements in the fashion claimed by the patent at issue. ...it can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does... because inventions in most, if not all, instances rely upon building blocks long since uncovered, and claimed discoveries almost of necessity will be combinations of what, in some sense, is already known.” (*KSR*, 550 U.S. at 417) Second, the proposed modification of the prior art must have had a reasonable expectation of success, determined from the vantage point of the skilled artisan at the time the invention was made. *Amgen Inc. v. Chugai Pharm. Co.*, 18 USPQ2d 1016, 1023 (Fed. Cir. 1991). Lastly, the prior art references must teach or suggest all the limitations of the claims. *In re Wilson*, 165 USPQ 494, 496 (C.C.P.A. 1970).

With regard to motivation to combine references, **MPEP 2143** discusses the requirements of a *prima facie* case of obviousness. First, there must be some suggestion or motivation to combine the reference teachings or to modify the reference, and second, there must be a reasonable expectation of success. Finally, the prior art reference or references when properly combined must teach or suggest all the claim limitations.

Regarding motivation to modify properly combined references, **MPEP 2143.01** states that a proposed modification cannot render the prior art unsatisfactory for its intended purpose. If it does, then there is no suggestion or motivation to make the proposed modification. Further, the proposed modification cannot change the principle operation of a reference.

Regarding *teaching away*, **MPEP 2141.02** states that prior art must be considered in its entirety, including disclosures that *teach away* from the claims. See also **MPEP 2145(X)(D)**. The Federal Circuit in *Takeda v. Alphapharm* found that the prior art taught away from the closest compound because the prior art in fact disclosed a broad selection of compounds where the closest prior art compound exhibited negative properties that would have led the skilled artisan away from that compound.

In *Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, 492 F. 3d 1350 (Fed. Cir. 2007), the Federal Circuit rejected Alphapharm's argument that the prior art would have led one of ordinary skill in the art to select compound b as a lead compound most promising to modify in order to improve its antidiabetic activity and thus potentially arrive at the claimed pioglitazone. The district court considered three references in reaching its determination, namely Takeda's '200 patent; Sodha II; and Takeda's '779 patent.

The district court found that Sodha II taught away from compound b and that any suggestion in the '779 patent to select compound b was essentially negated by the disclosure of Sodha II in view of the more exhaustive and reliable scientific analysis presented by Sodha II and the teaching away. Accordingly, the Federal Circuit accorded more weight to the Sodha II reference.

Present claim 28 recites the following "A pharmaceutical composition for parenteral administration, comprising: a therapeutically effective amount of a protein or polypeptide selected from the group consisting of Factor VIIa for treating trauma bleeding in hemophilia patients, granulocyte colony-stimulating factor (G-CSF), granulocyte macrophage colony-stimulating factor (GM-CSF), interferon γ , glucagon-like peptide 1 (GLP-1), and glatiramer acetate; and one or more colloidal particles comprising approximately 1-20 mole percent of an amphipathic lipid derivatized with a biocompatible hydrophilic polymer, wherein the protein or polypeptide is non-covalently bound to the one or more colloidal particles and the protein or polypeptide is not encapsulated in the one or more colloidal particles.

Baru describes pharmaceutical compositions comprising Factor VIII and neutral liposomes.

It is submitted that a proper case of *prima facie* obviousness has not been established because the combination of Baru with Martin is improper because there is no suggestion or motivation to combine the reference teachings or to modify the reference. See **MPEP 2143**.

More specifically, the proteins or polypeptides of Baru are ***not encapsulated*** in the colloidal particles. Martin, on the other hand, describes liposome compositions

which “contain the therapeutic compound in *liposome-entrapped form*” (abstract). The skilled artisan would not combine these references since they teach liposome compositions of significantly different structure, one (Baru) in which the protein is outside the liposome and one (Martin) in which the protein is inside the liposome. Thus, the Examiner is incorrect when he states (page 13, line 9): “The formulations of the prior arts are similar...”. The formulations of Baru and Martin are not similar and are in fact completely different. The skilled artisan when reviewing Baru that describes small liposomes where the protein is not encapsulated in the liposome, would have no motivation to look to art describing larger liposomes having sufficiently high encapsulation volumes and encapsulated proteins, i.e., Martin. Likewise, the skilled artisan when reviewing Martin that describes encapsulated proteins, would have no motivation to look to art describing liposomes where the protein is not encapsulated, i.e., Baru.

In addition, although Baru discloses the coagulation factors Factor VIII, prothrombin, Factor X and Factor V, this does *not* make obvious the use of Factor VIIa in the present claims. These factors have completely different physico-chemical properties, as shown in the following table. It is these properties, and not the therapeutic use, which determine whether the protein will be active when bound to the colloidal particle, and whether the half life will be extended. Since FVIIa has such a short half-life, it was not obvious that the presently described composition would be successful in extending its half-life.

| Protein | MW (Da) | half-life (Hr.) |
|-------------|---------|-----------------|
| Factor VIII | 330,000 | 10-12 |
| prothrombin | 72,000 | 60 |
| Factor X | 58,500 | 48-72 |
| Factor V | 330,000 | 36 |
| Factor VIIa | 50,000 | 2.3 |

Furthermore, the Examiner states that Martin teaches the supplementation of cholesterol in the composition (bottom of page 11). However, in truth, Martin **teaches away** from using cholesterol. Martin states (col. 6, lines 3-9): "In general, cholesterol may be **less tightly anchored** to a lipid bilayer membrane, particularly when derivatized with a high molecular weight polyalkylether, and therefore **be less effective** in promoting liposome evasion of the RES in the bloodstream." (emphasis added - JP). Thus, Martin teaches that cholesterol would be less effective than other lipids.

Ishikawa and Igari merely teach that G-CSF has a short biological half life, but do not teach how this problem may be overcome.

In view of the foregoing, it is submitted that nothing in Baru et al., Martin, Ishikawa and Igari, taken alone or together, renders the presently claimed subject matter obvious within the meaning of 35 USC § 103. Accordingly, the Examiner is respectfully requested to withdraw this rejection.

V. ***At page 14 of the Official Action, claims 28-34, 36-42, 57, 59-60, 62-65, 67-68 and 73-74 have been rejected under 35 USC § 103(a) as being unpatentable over Baru M in view of Martin et al. and Chen or Galloway.***

The Examiner asserts that “it would have been obvious to one of ordinary skill in the art to combine the teachings of Baru et al., Martin et al. patents, Chen et al. or Galloway et al., since Baru teaches a pharmaceutical composition for parenteral administration comprising a therapeutically effective amount of a protein or polypeptide and substantially neutral colloidal particles, and teaches that the term ‘proteins or polypeptides capable of externally binding said colloidal particles’ includes proteins and polypeptides which, similarly to FVIII, and non-limiting examples of such proteins are coagulation factors such as prothrombin, Factor X and Factor V. Martin et al. teach Interferon gamma, G-CSF, M-CSF, GM-CSF, and other proteins that are incorporated with the liposomes.” The Examiner also states that “Therefore, it would have been obvious...to use the liposomes of Baru to increase the half life of these [Chen/Galloway] compounds.”

In view of the remarks set forth herein, this rejection is respectfully traversed.

To establish a *prima facie* case of obviousness, the PTO must satisfy three requirements. First, as the U.S. Supreme Court very recently held in *KSR International Co. v. Teleflex Inc. et al.*, 550 U.S. 398 (2007), “a court must ask whether the improvement is more than the predictable use of prior art elements according to their established functions. ...it [may] be necessary for a court to look to interrelated teachings of multiple patents; the effects of demands known to the design community or present in the marketplace; and the background knowledge possessed by a person having ordinary skill in the art, all in order to determine whether there was an apparent

reason to combine the known elements in the fashion claimed by the patent at issue. ...it can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does... because inventions in most, if not all, instances rely upon building blocks long since uncovered, and claimed discoveries almost of necessity will be combinations of what, in some sense, is already known." (KSR, 550 U.S. at 417) Second, the proposed modification of the prior art must have had a reasonable expectation of success, determined from the vantage point of the skilled artisan at the time the invention was made. *Amgen Inc. v. Chugai Pharm. Co.*, 18 USPQ2d 1016, 1023 (Fed. Cir. 1991). Lastly, the prior art references must teach or suggest all the limitations of the claims. *In re Wilson*, 165 USPQ 494, 496 (C.C.P.A. 1970).

With regard to motivation to combine references, **MPEP 2143** discusses the requirements of a *prima facie* case of obviousness. First, there must be some suggestion or motivation to combine the reference teachings or to modify the reference, and second, there must be a reasonable expectation of success. Finally, the prior art reference or references when properly combined, must teach or suggest all the claim limitations.

Regarding motivation to modify properly combined references, **MPEP 2143.01** states that a proposed modification cannot render the prior art unsatisfactory for its intended purpose. If it does, then there is no suggestion or motivation to make the proposed modification. Further, the proposed modification cannot change the principle operation of a reference.

Regarding *teaching away*, MPEP 2141.02 states that prior art must be considered in its entirety, including disclosures that *teach away* from the claims. See also MPEP 2145(X)(D). The Federal Circuit in *Takeda v. Alphapharm* found that the prior art taught away from the closest compound because the prior art in fact disclosed a broad selection of compounds where the closest prior art compound exhibited negative properties that would have led the skilled artisan away from that compound.

In *Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, 492 F. 3d 1350 (Fed. Cir. 2007), the Federal Circuit rejected Alphapharm's argument that the prior art would have led one of ordinary skill in the art to select compound b as a lead compound most promising to modify in order to improve its antidiabetic activity and thus potentially arrive at the claimed pioglitazone. The district court considered three references in reaching its determination, namely Takeda's '200 patent; Sodha II; and Takeda's '779 patent. The district court found that Sodha II taught away from compound b and that any suggestion in the '779 patent to select compound b was essentially negated by the disclosure of Sodha II in view of the more exhaustive and reliable scientific analysis presented by Sodha II and the teaching away. Accordingly, the Federal Circuit accorded more weight to the Sodha II reference.

Present claim 28 recites the following "A pharmaceutical composition for parenteral administration, comprising: a therapeutically effective amount of a protein or polypeptide selected from the group consisting of Factor VIIa for treating trauma bleeding in hemophilia patients, granulocyte colony-stimulating factor (G-CSF), granulocyte macrophage colony-stimulating factor (GM-CSF), interferon γ , glucagon-like peptide 1 (GLP-1), and glatiramer acetate; and one or more colloidal particles comprising

approximately 1-20 mole percent of an amphipathic lipid derivatized with a biocompatible hydrophilic polymer, wherein the protein or polypeptide is non-covalently bound to the one or more colloidal particles and the protein or polypeptide is not encapsulated in the one or more colloidal particles.

Baru describes pharmaceutical compositions comprising Factor VIII and neutral liposomes.

It is submitted that a proper case of *prima facie* obviousness has not been established because the combination of Baru with Martin is improper because there is no suggestion or motivation to combine the reference teachings or to modify the reference. See **MPEP 2143**.

More specifically, the proteins or polypeptides of Baru are *not encapsulated* in the colloidal particles. Martin, on the other hand, describes liposome compositions which “contain the therapeutic compound in *liposome-entrapped form*” (abstract). The skilled artisan would not combine these references since they teach liposome compositions of significantly different structure, one (Baru) in which the protein is outside the liposome and one (Martin) in which the protein is inside the liposome. Thus, the Examiner is incorrect when he states (page 13, line 9): “The formulations of the prior arts are similar...”. The formulations of Baru and Martin are not similar and are in fact completely different. The skilled artisan when reviewing Baru that describes small liposomes (0.05 to 0.1 microns) where the protein is not encapsulated in the liposome, would have no motivation to look to art describing larger liposomes having sufficiently high encapsulation volumes and encapsulated proteins, i.e., Martin. Likewise, the skilled artisan when reviewing Martin that describes encapsulated proteins, would have

no motivation to look to art describing liposomes where the protein is not encapsulated, i.e., Baru.

In addition, although Baru discloses the coagulation factors Factor VIII, prothrombin, Factor X and Factor V, this does **not** make obvious the use of Factor VIIa in the present claims. These factors have completely different physico-chemical properties, as shown in the following table. It is these properties, and not the therapeutic use, which determine whether the protein will be active when bound to the colloidal particle, and whether the half life will be extended. Since FVIIa has such a short half-life, it was not obvious that the presently described composition would be successful in extending its half-life.

| Protein | MW (Da) | half-life (Hr.) |
|-------------|---------|-----------------|
| Factor VIII | 330,000 | 10-12 |
| prothrombin | 72,000 | 60 |
| Factor X | 58,500 | 48-72 |
| Factor V | 330,000 | 36 |
| Factor VIIa | 50,000 | 2.3 |

Furthermore, the Examiner states that Martin teaches the supplementation of cholesterol in the composition (bottom of page 11). However, in truth, Martin **teaches away** from using cholesterol. Martin states (col. 6, lines 3-9): "In general, cholesterol may be **less tightly anchored** to a lipid bilayer membrane, particularly when derivatized with a high molecular weight polyalkylether, and therefore **be less effective** in promoting liposome evasion of the RES in the bloodstream." (emphasis added - JP). Thus, Martin teaches that cholesterol would be less effective than other lipids.

Chen and Galloway merely teach that GLP-1 has a short biological half life, but do not teach how this problem may be overcome.

In view of the foregoing, it is submitted that nothing in Baru et al., Martin, Chen and Galloway, taken alone or together, renders the presently claimed subject matter obvious within the meaning of 35 USC § 103. Accordingly, the Examiner is respectfully requested to withdraw this rejection.

VI. At page 16 of the Official Action, claims 28-34, 36-42, 47, 50, 53, 57, 59-60, 62-65, 67-68 and 73-74 have been rejected under 35 USC § 103(a) as being unpatentable over Baru M in view of Martin et al. and Heldman et al. as evidenced by <http://www.copaxone.com/>, prescribing information and further in view of Braxton.

The Examiner asserts that "it would have been obvious to one of ordinary skill in the art to combine the teachings of Baru et al., Martin et al. patents, Heldman et al. and Braxton patent, since Baru teaches a pharmaceutical composition for parenteral administration comprising a therapeutically effective amount of a protein or polypeptide and substantially neutral colloidal particles, and teaches that the term 'proteins or polypeptides capable of externally binding said colloidal particles' includes proteins and polypeptides which, similarly to FVIII, and non-limiting examples of such proteins are coagulation factors such as prothrombin, Factor X and Factor V. Martin et al. teach Interferon gamma, G-CSF, M-CSF, GM-CSF, and other proteins that are incorporated with the liposomes." The Examiner also states that "Furthermore, Heldman et al teach that Copaxone®, insulin, herceptin (monoclonal antibody) all have very short lifetime at the delivery site. As evidenced by www.copaxone.com multiple sclerosis (MS) is known to be treatable by Copaxone®. Therefore, it would have been obvious to one of

ordinary skill in the art to treat multiple sclerosis with a pharmaceutical composition comprising Copaxone® non-covalently bound to colloidal particle. Further, it would have been obvious to one of ordinary skill in the art to use the liposomes of Baru to increase the half life of these compounds...."

In view of the remarks set forth herein, this rejection is respectfully traversed.

To establish a *prima facie* case of obviousness, the PTO must satisfy three requirements. First, as the U.S. Supreme Court very recently held in *KSR International Co. v. Teleflex Inc. et al.*, 550 U.S. 398 (2007), "a court must ask whether the improvement is more than the predictable use of prior art elements according to their established functions. ...it [may] be necessary for a court to look to interrelated teachings of multiple patents; the effects of demands known to the design community or present in the marketplace; and the background knowledge possessed by a person having ordinary skill in the art, all in order to determine whether there was an apparent reason to combine the known elements in the fashion claimed by the patent at issue. ...it can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does... because inventions in most, if not all, instances rely upon building blocks long since uncovered, and claimed discoveries almost of necessity will be combinations of what, in some sense, is already known." (*KSR*, 550 U.S. at 417) Second, the proposed modification of the prior art must have had a reasonable expectation of success, determined from the vantage point of the skilled artisan at the time the invention was made. *Amgen Inc. v. Chugai Pharm. Co.*, 18 USPQ2d 1016, 1023 (Fed. Cir. 1991).

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at the claimed pioglitazone. The district court considered three references in reaching its determination, namely Takeda's '200 patent; Sodha II; and Takeda's '779 patent. The district court found that Sodha II taught away from compound b and that any suggestion in the '779 patent to select compound b was essentially negated by the disclosure of Sodha II in view of the more exhaustive and reliable scientific analysis presented by Sodha II and the teaching away. Accordingly, the Federal Circuit accorded more weight to the Sodha II reference.

Present claim 28 recites the following "A pharmaceutical composition for parenteral administration, comprising: a therapeutically effective amount of a protein or polypeptide selected from the group consisting of Factor VIIa for treating trauma bleeding in hemophilia patients, granulocyte colony-stimulating factor (G-CSF), granulocyte macrophage colony-stimulating factor (GM-CSF), interferon γ , glucagon-like peptide 1 (GLP-1), and glatiramer acetate; and one or more colloidal particles comprising approximately 1-20 mole percent of an amphipathic lipid derivatized with a biocompatible hydrophilic polymer, wherein the protein or polypeptide is non-covalently bound to the one or more colloidal particles and the protein or polypeptide is not encapsulated in the one or more colloidal particles.

Baru describes pharmaceutical compositions comprising Factor VIII and neutral liposomes.

It is submitted that a proper case of *prima facie* obviousness has not been established because the combination of Baru with Martin is improper because there is no suggestion or motivation to combine the reference teachings or to modify the reference. See MPEP 2143.

More specifically, the proteins or polypeptides of Baru are *not encapsulated* in the colloidal particles. Martin, on the other hand, describes liposome compositions which “contain the therapeutic compound in *liposome-entrapped form*” (abstract). The skilled artisan would not combine these references since they teach liposome compositions of significantly different structure, one (Baru) in which the protein is outside the liposome and one (Martin) in which the protein is inside the liposome. Thus, the Examiner is incorrect when he states (page 13, line 9): “The formulations of the prior arts are similar...”. The formulations of Baru and Martin are not similar and are in fact completely different. The skilled artisan when reviewing Baru that describes small liposomes (0.05 to 0.1 microns) where the protein is not encapsulated in the liposome, would have no motivation to look to art describing larger liposomes having sufficiently high encapsulation volumes and encapsulated proteins, i.e., Martin. Likewise, the skilled artisan when reviewing Martin that describes encapsulated proteins, would have no motivation to look to art describing liposomes where the protein is not encapsulated, i.e., Baru.

In addition, although Baru discloses the coagulation factors Factor VIII, prothrombin, Factor X and Factor V, this does *not* make obvious the use of Factor VIIa in the present claims. These factors have completely different physico-chemical properties, as shown in the following table. It is these properties, and not the therapeutic use, which determine whether the protein will be active when bound to the colloidal particle, and whether the half life will be extended. Since FVIIa has such a short half-life, it was not obvious that the presently described composition would be successful in extending its half-life.

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| Factor V | 330,000 | 36 |
| Factor VIIa | 50,000 | 2.3 |

Furthermore, the Examiner states that Martin teaches the supplementation of cholesterol in the composition (bottom of page 11). However, in truth, Martin **teaches away** from using cholesterol. Martin states (col. 6, lines 3-9): "In general, cholesterol may be **less tightly anchored** to a lipid bilayer membrane, particularly when derivatized with a high molecular weight polyalkylether, and therefore **be less effective** in promoting liposome evasion of the RES in the bloodstream." (emphasis added - JP). Thus, Martin teaches that cholesterol would be less effective than other lipids.

Heldman describes vesicles and liposomes made from amphiphilic derivatives for site-directed delivery of therapeutic agents and specific release thereof at a target tissue (paragraph [0001]). The vesicles and liposomes can be used for encapsulating drugs and delivering them, while being encapsulated, to target organs [0019]. Thus, Heldman, similarly to Martin, teaches that the proteins are entrapped within the liposomes, and not outside the liposome as presently claimed.

Furthermore, the liposomes of Heldman have a completely different lipid component as compared to the present colloidal particles. The liposomes of Heldman have no amphipathic lipid derivatized with a biocompatible hydrophilic polymer, as presently claimed.

The internet citation is cited as teaching that MS is treatable with Copaxone®. Nothing is taught regarding how to extend the biological half life of Copaxone®.

Braxton describes that PEGylation of certain proteins increases their half lives. Braxton does not teach or allude to the presently claimed composition.

In view of the foregoing, it is submitted that nothing in Baru et al., Martin, Heldman, www.copaxone.com and Braxton, taken alone or together, renders the presently claimed subject matter obvious within the meaning of 35 USC § 103. Accordingly, the Examiner is respectfully requested to withdraw this rejection.

VII. At page 18 of the Official Action, claims 28-34, 36-42, 47, 54, 57-60, 62-65, 67-69 and 71-74 have been rejected under 35 USC § 103(a) as being unpatentable over Baru M in view of Martin et al. and Braxton and Papatheodoridis et al.

The Examiner asserts that "it would have been obvious to one of ordinary skill in the art to combine the teachings of Baru et al., Martin et al. patents, Braxton patent and Papatheodoridis reference, since Baru teaches a pharmaceutical composition for parenteral administration comprising a therapeutically effective amount of a protein or polypeptide and substantially neutral colloidal particles, and teaches that the term 'proteins or polypeptides capable of externally binding said colloidal particles' includes proteins and polypeptides which, similarly to FVIII, and non-limiting examples of such proteins are coagulation factors such as prothrombin, Factor X and Factor V. Martin et al. teach Interferon gamma, G-CSF, M-CSF, GM-CSF, and other proteins that are incorporated with the liposomes." The Examiner also states that "Furthermore, Braxton reference teaches proteins for which an increase half-life has been accomplished by

PEGylation of the protein include: hGH,...Papatheodoridis et al. further teaches that factor VII has the shortest half life...it would have been obvious to one of ordinary skill in the art to use the liposomes of Baru to increase the half life of these compounds...."

In view of the remarks set forth herein, this rejection is respectfully traversed.

To establish a *prima facie* case of obviousness, the PTO must satisfy three requirements. First, as the U.S. Supreme Court very recently held in *KSR International Co. v. Teleflex Inc. et al.*, 550 U.S. 398 (2007), "a court must ask whether the improvement is more than the predictable use of prior art elements according to their established functions. ...it [may] be necessary for a court to look to interrelated teachings of multiple patents; the effects of demands known to the design community or present in the marketplace; and the background knowledge possessed by a person having ordinary skill in the art, all in order to determine whether there was an apparent reason to combine the known elements in the fashion claimed by the patent at issue. ...it can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does... because inventions in most, if not all, instances rely upon building blocks long since uncovered, and claimed discoveries almost of necessity will be combinations of what, in some sense, is already known." (*KSR*, 550 U.S. at 417) Second, the proposed modification of the prior art must have had a reasonable expectation of success, determined from the vantage point of the skilled artisan at the time the invention was made. *Amgen Inc. v. Chugai Pharm. Co.*, 18 USPQ2d 1016, 1023 (Fed. Cir. 1991). Lastly, the prior art references must teach or suggest all the limitations of the claims. *In re Wilson*, 165 USPQ 494, 496 (C.C.P.A. 1970).

With regard to motivation to combine references, **MPEP 2143** discusses the requirements of a *prima facie* case of obviousness. First, there must be some suggestion or motivation to combine the reference teachings or to modify the reference, and second, there must be a reasonable expectation of success. Finally, the prior art reference or references when properly combined, must teach or suggest all the claim limitations.

Regarding motivation to modify properly combined references, **MPEP 2143.01** states that a proposed modification cannot render the prior art unsatisfactory for its intended purpose. If it does, then there is no suggestion or motivation to make the proposed modification. Further, the proposed modification cannot change the principle operation of a reference.

Regarding *teaching away*, **MPEP 2141.02** states that prior art must be considered in its entirety, including disclosures that *teach away* from the claims. See also **MPEP 2145(X)(D)**. The Federal Circuit in *Takeda v. Alphapharm* found that the prior art taught away from the closest compound because the prior art in fact disclosed a broad selection of compounds where the closest prior art compound exhibited negative properties that would have led the skilled artisan away from that compound.

In *Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, 492 F. 3d 1350 (Fed. Cir. 2007), the Federal Circuit rejected Alphapharm's argument that the prior art would have led one of ordinary skill in the art to select compound b as a lead compound most promising to modify in order to improve its antidiabetic activity and thus potentially arrive at the claimed pioglitazone. The district court considered three references in reaching its determination, namely Takeda's '200 patent; Sodha II; and Takeda's '779 patent.

The district court found that Sodha II taught away from compound b and that any suggestion in the '779 patent to select compound b was essentially negated by the disclosure of Sodha II in view of the more exhaustive and reliable scientific analysis presented by Sodha II and the teaching away. Accordingly, the Federal Circuit accorded more weight to the Sodha II reference.

Present claim 28 recites the following "A pharmaceutical composition for parenteral administration, comprising: a therapeutically effective amount of a protein or polypeptide selected from the group consisting of Factor VIIa for treating trauma bleeding in hemophilia patients, granulocyte colony-stimulating factor (G-CSF), granulocyte macrophage colony-stimulating factor (GM-CSF), interferon γ , glucagon-like peptide 1 (GLP-1), and glatiramer acetate; and one or more colloidal particles comprising approximately 1-20 mole percent of an amphipathic lipid derivatized with a biocompatible hydrophilic polymer, wherein the protein or polypeptide is non-covalently bound to the one or more colloidal particles and the protein or polypeptide is not encapsulated in the one or more colloidal particles.

Baru describes pharmaceutical compositions comprising Factor VIII and neutral liposomes.

It is submitted that a proper case of *prima facie* obviousness has not been established because the combination of Baru with Martin is improper because there is no suggestion or motivation to combine the reference teachings or to modify the reference. See MPEP 2143.

More specifically, the proteins or polypeptides of Baru are *not encapsulated* in the colloidal particles. Martin, on the other hand, describes liposome compositions

which "contain the therapeutic compound in *liposome-entrapped form*" (abstract). The skilled artisan would not combine these references since they teach liposome compositions of significantly different structure, one (Baru) in which the protein is outside the liposome and one (Martin) in which the protein is inside the liposome. Thus, the Examiner is incorrect when he states (page 13, line 9): "The formulations of the prior arts are similar...". The formulations of Baru and Martin are not similar and are in fact completely different. The skilled artisan when reviewing Baru that describes small liposomes (0.05 to 0.1 microns) where the protein is not encapsulated in the liposome, would have no motivation to look to art describing larger liposomes having sufficiently high encapsulation volumes and encapsulated proteins, i.e., Martin. Likewise, the skilled artisan when reviewing Martin that describes encapsulated proteins, would have no motivation to look to art describing liposomes where the protein is not encapsulated, i.e., Baru.

In addition, although Baru discloses the coagulation factors Factor VIII, prothrombin, Factor X and Factor V, this does *not* make obvious the use of Factor VIIa in the present claims. These factors have completely different physico-chemical properties, as shown in the following table. It is these properties, and not the therapeutic use, which determine whether the protein will be active when bound to the colloidal particle, and whether the half life will be extended. Since FVIIa has such a short half-life, it was not obvious that the presently described composition would be successful in extending its half-life.

| Protein | MW (Da) | half-life (Hr.) |
|-------------|---------|-----------------|
| Factor VIII | 330,000 | 10-12 |
| prothrombin | 72,000 | 60 |
| Factor X | 58,500 | 48-72 |
| Factor V | 330,000 | 36 |
| Factor VIIa | 50,000 | 2.3 |

Furthermore, the Examiner states that Martin teaches the supplementation of cholesterol in the composition (bottom of page 11). However, in truth, Martin **teaches away** from using cholesterol. Martin states (col. 6, lines 3-9): "In general, cholesterol may be *less tightly anchored* to a lipid bilayer membrane, particularly when derivatized with a high molecular weight polyalkylether, and therefore **be less effective** in promoting liposome evasion of the RES in the bloodstream." (emphasis added - JP). Thus, Martin teaches that cholesterol would be less effective than other lipids.

Braxton describes that PEGylation of certain proteins increases their half lives. Braxton does not teach or allude to the presently claimed composition.

Papatheodoridis is merely cited as teaching that Factor VII has a short half life. However, Factor VII is **not** Factor VIIa. FVII is a **single-chain protein**. Once bound to Tissue Factor, FVII is activated to FVIIa by **different** proteases. FVIIa consists of **two chains** linked via a single disulfide bond (Cys 135 to Cys 262). In addition:

| | type of protein | half-life (hr) |
|-------------|-----------------|----------------|
| Factor VII | zymogen | 4-6 |
| Factor VIIa | enzyme | 2.3 |

In view of the foregoing, it is submitted that nothing in Baru et al., Martin, Braxton, and Papatheodoridis, taken alone or together, renders the presently claimed

subject matter obvious within the meaning of 35 USC § 103. Accordingly, the Examiner is respectfully requested to withdraw this rejection.

VIII. At page 18 of the Official Action, claims 35, 61 and 66 have been rejected under 35 USC § 103(a) as being unpatentable over Baru M in view of Martin et al. and Ishikawa et al. and Igari et al. and further in view of Zalipsky.

Claims 35, 61 and 66 have been cancelled without prejudice or disclaimer. Accordingly, this rejection is moot with regard to claims 35, 61 and 66.

IX. At page 23 of the Official Action, claim 70 has been rejected under 35 USC § 103(a) as being unpatentable over Baru M in view of Martin et al. and Braxton and Papatheodoridis and further in view of Zalipsky.

Claim 70 has been cancelled without prejudice or disclaimer. Accordingly, this rejection is moot with regard to claim 70

CONCLUSION

In view of the foregoing, Applicant submits that the application is in condition for immediate allowance. Early notice to that effect is earnestly solicited. The Examiner is invited to contact the undersigned attorney if it is believed that such contact will expedite the prosecution of the application.

In the event this paper is not timely filed, Applicants petition for an appropriate extension of time. Please charge any fee deficiency or credit any overpayment to Deposit Account No. 14-0112.

Respectfully submitted,

THE NATH LAW GROUP



Gary M. Nath
Registration No. 26,965
Susanne M. Hopkins
Registration No. 33,247
Customer No. 20259

Date: December 28, 2009
THE NATH LAW GROUP
112 South West Street
Alexandria, VA 22314
Tel: (703) 548-NATH
Fax: (703) 683-8396

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed
to use COPAXONE® safely and effectively.
See full prescribing information for COPAXONE.

COPAXONE (glatiramer acetate injection) solution for subcutaneous injection
Initial U.S. Approval: 1996

RECENT MAJOR CHANGES

Indications and Usage (1) 2/2009

INDICATIONS AND USAGE

COPAXONE is indicated for reduction of the frequency of relapses in patients with Relapsing-Remitting Multiple Sclerosis, including patients who have experienced a first clinical episode and have MRI features consistent with multiple sclerosis.

DOSAGE AND ADMINISTRATION

- For subcutaneous injection only (2.1)
- Recommended dose: 20 mg/day (2.1)
- Before use, allow the solution to warm to room temperature (2.2)

DOSAGE FORMS AND STRENGTHS

- Prefilled syringe containing 1 mL solution with 20 mg of glatiramer acetate (3)

CONTRAINDICATIONS

Known hypersensitivity to glatiramer acetate or mannitol (4)

WARNINGS AND PRECAUTIONS

- Immediate Post-Injection Reaction (flushing, chest pain, palpitations, anxiety, dyspnea, throat constriction, and/or urticaria), generally transient and self-limiting (5.1)
- Chest pain, usually transient (5.2)
- Lipoatrophy and skin necrosis may occur. Instruct patient in proper injection technique and to rotate injection sites daily (5.3)
- COPAXONE can modify immune response (5.4)

ADVERSE REACTIONS

- In controlled studies, most common adverse reactions ($\geq 10\%$ and ≥ 1.5 times higher than placebo) were: injection site reactions, vasodilatation, rash, dyspnea, and chest pain (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact TEVA at 1-800-221-4026 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

USE IN SPECIFIC POPULATIONS

- Nursing Mothers: It is not known if COPAXONE is excreted in human milk (8.3)
- Pediatric Use: The safety and effectiveness of COPAXONE have not been established in patients under 18 years of age (8.4)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: [2/2009]

FULL PRESCRIBING INFORMATION: CONTENTS*

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2 DOSAGE AND ADMINISTRATION

- 2.1 Recommended Dose
- 2.2 Instructions for Use

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

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*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION COPAXONE (glatiramer acetate injection)

1 INDICATIONS AND USAGE

COPAXONE is indicated for reduction of the frequency of relapses in patients with Relapsing-Remitting Multiple Sclerosis (RRMS), including patients who have experienced a first clinical episode and have MRI features consistent with multiple sclerosis.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dose

COPAXONE is for subcutaneous use only. Do not administer intravenously. The recommended dose of COPAXONE is 20 mg/day.

2.2 Instructions for Use

Remove one blister that contains the syringe from the COPAXONE prefilled syringes package. Since this product should be refrigerated, let the prefilled syringe stand at room temperature for 20 minutes to allow the solution to warm to room temperature. Inspect the COPAXONE syringe visually for particulate matter and discoloration prior to administration, whenever solution and container permit. The solution in the syringe should appear clear, colorless to slightly yellow. If particulate matter or discoloration is observed, discard the COPAXONE syringe.

Areas for self-injection include arms, abdomen, hips, and thighs. The prefilled syringe is for single use only. Discard unused portions.

3 DOSAGE FORMS AND STRENGTHS

Single-use prefilled syringe containing 1 mL solution with 20 mg of glatiramer acetate and 40 mg of mannitol.

4 CONTRAINDICATIONS

COPAXONE is contraindicated in patients with known hypersensitivity to glatiramer acetate or mannitol.

5 WARNINGS AND PRECAUTIONS

5.1 Immediate Post-Injection Reaction

Approximately 16% of patients exposed to COPAXONE in the 5 placebo-controlled trials compared to 4% of those on placebo experienced a constellation of symptoms immediately after injection that included at least two of the following: flushing, chest pain, palpitations, anxiety, dyspnea, constriction of the throat, and urticaria. The symptoms were generally transient and self-limited and did not require treatment. In general, these symptoms have their onset several months after the initiation of treatment, although they may occur earlier, and a given patient may experience one or several episodes of these symptoms. Whether or not any of these symptoms actually represent a specific syndrome is uncertain. During the postmarketing period, there have been reports of patients with similar symptoms who received emergency medical care.

Whether an immunologic or nonimmunologic mechanism mediates these episodes, or whether several similar episodes seen in a given patient have identical mechanisms, is unknown.

5.2 Chest Pain

Approximately 13% of COPAXONE patients in the 5 placebo-controlled studies compared to 6% of placebo patients experienced at least one episode of what was described as transient chest pain. While some of these episodes occurred in the context of the Immediate Post-Injection Reaction described above, many did not. The temporal relationship of this chest pain to an injection of COPAXONE was not always known. The pain was transient (usually lasting only a few minutes), often unassociated with other symptoms, and appeared to have no clinical sequelae. Some patients experienced more than one such episode, and episodes usually began at least 1 month after the initiation of treatment. The pathogenesis of this symptom is unknown.

5.3 Lipoatrophy and Skin Necrosis

At injection sites, localized lipoatrophy and, rarely, injection site skin necrosis have been reported during the postmarketing experience. Lipoatrophy may occur at various times after treatment onset (sometimes after several months) and is thought to be permanent. There is no known therapy for lipoatrophy. To assist in possibly minimizing these events, the patient should be advised to follow proper injection technique and to rotate injection sites daily.

5.4 Potential Effects on Immune Response

Because COPAXONE can modify immune response, it may interfere with immune functions. For example, treatment with COPAXONE may interfere with the recognition of foreign antigens in a way that would undermine the body's tumor surveillance and its defenses against infection. There is no evidence that COPAXONE does this, but there has not been a systematic evaluation of this risk. Because COPAXONE is an antigenic material, it is possible that its use may lead to the induction of host responses that are untoward, but systematic surveillance for these effects has not been undertaken.

Although COPAXONE is intended to minimize the autoimmune response to myelin, there is the possibility that continued alteration of cellular immunity due to chronic treatment with COPAXONE may result in untoward effects.

Glatiramer acetate-reactive antibodies are formed in most patients exposed to daily treatment with the recommended dose. Studies in both the rat and monkey have suggested that immune complexes are deposited in the renal glomeruli. Furthermore, in a controlled trial of 125 RRMS patients given COPAXONE, 20 mg, subcutaneously every day for 2 years, serum IgG levels reached at least 3 times baseline values in 80% of patients by 3 months of initiation of treatment. By 12 months of treatment, however, 30% of patients still had IgG levels at least 3 times baseline val-

ues, and 90% had levels above baseline by 12 months. The antibodies are exclusively of the IgG subtype and predominantly of the IgG-1 subtype. No IgE type antibodies could be detected in any of the 94 sera tested; nevertheless, anaphylaxis can be associated with the administration of most any foreign substance, and therefore, this risk cannot be excluded.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

Incidence in Controlled Clinical Trials

Among 563 patients treated with COPAXONE in blinded placebo controlled trials, approximately 5% of the subjects discontinued treatment because of an adverse reaction. The adverse reactions most commonly associated with discontinuation were: injection site reactions, dyspnea, urticaria, vasodilatation, and hypersensitivity. The most common adverse reactions were: injection site reactions, vasodilatation, rash, dyspnea, and chest pain.

Table 1 lists treatment-emergent signs and symptoms that occurred in at least 2% of patients treated with COPAXONE in the placebo-controlled trials. These signs and symptoms were numerically more common in patients treated with COPAXONE than in patients treated with placebo. Adverse reactions were usually mild in intensity.

Table 1: Adverse reactions in controlled clinical trials with an incidence $\geq 2\%$ of patients and more frequent with COPAXONE than with placebo

| | | GA 20 mg (N=563) | Placebo (N=564) |
|---|---------------------------------|---------------------|--------------------|
| Blood And Lymphatic System Disorders | Lymphadenopathy | 7% | 3% |
| Cardiac Disorders | Palpitations | 9% | 4% |
| | Tachycardia | 5% | 2% |
| Eye Disorders | Eye Disorder | 3% | 1% |
| | Diplopia | 3% | 2% |
| Gastrointestinal Disorders | Nausea | 15% | 11% |
| | Vomiting | 7% | 4% |
| | Dysphagia | 2% | 1% |
| General Disorders And Administration Site Conditions | Injection Site Erythema | 43% | 10% |
| | Injection Site Pain | 40% | 20% |
| | Injection Site Pruritus | 27% | 4% |
| | Injection Site Mass | 26% | 6% |
| | Asthenia | 22% | 21% |
| | Pain | 20% | 17% |
| | Injection Site Edema | 19% | 4% |
| | Chest Pain | 13% | 6% |
| | Injection Site Inflammation | 9% | 1% |
| | Edema | 8% | 2% |
| | Injection Site Reaction | 8% | 1% |
| | Pyrexia | 6% | 5% |
| | Injection Site Hypersensitivity | 4% | 0% |
| | Local Reaction | 3% | 1% |
| | Chills | 3% | 1% |
| | Face Edema | 3% | 1% |
| | Edema Peripheral | 3% | 2% |
| | Injection Site Fibrosis | 2% | 1% |
| | Injection Site Atrophy* | 2% | 0% |
| Immune System Disorders | Hypersensitivity | 3% | 2% |
| Infections And Infestations | Infection | 30% | 28% |
| | Influenza | 14% | 13% |
| | Rhinitis | 7% | 5% |
| | Bronchitis | 6% | 5% |
| | Gastroenteritis | 6% | 4% |
| | Vaginal Candidiasis | 4% | 2% |
| Metabolism And Nutrition Disorders | Weight Increased | 3% | 1% |
| Musculoskeletal And Connective Tissue Disorders | Back Pain | 12% | 10% |
| Neoplasms Benign, Malignant And Unspecified (Incl Cysts And Polyps) | Benign Neoplasm of Skin | 2% | 1% |

| <i>Continued</i> | | GA 20 mg (N=563) | Placebo (N=564) |
|---|---------------------|---------------------|--------------------|
| Nervous System Disorders | Tremor | 4% | 2% |
| | Migraine | 4% | 2% |
| | Syncope | 3% | 2% |
| | Speech Disorder | 2% | 1% |
| Psychiatric Disorders | Anxiety | 13% | 10% |
| | Nervousness | 2% | 1% |
| Renal And Urinary Disorders | Micturition Urgency | 5% | 4% |
| Respiratory, Thoracic And Mediastinal Disorders | Dyspnea | 14% | 4% |
| | Cough | 6% | 5% |
| | Laryngospasm | 2% | 1% |
| Skin And Subcutaneous Tissue Disorders | Rash | 19% | 11% |
| | Hyperhidrosis | 7% | 5% |
| | Pruritus | 5% | 4% |
| | Urticaria | 3% | 1% |
| | Skin Disorder | 3% | 1% |
| Vascular Disorders | Vasodilatation | 20% | 5% |

*Injection site atrophy comprises terms relating to localized lipoatrophy at injection site

Adverse reactions which occurred only in 4-5 more subjects in the COPAXONE group than in the placebo group (less than 1% difference), but for which a relationship to COPAXONE could not be excluded, were arthralgia and herpes simplex.

Laboratory analyses were performed on all patients participating in the clinical program for COPAXONE. Clinically significant laboratory values for hematology, chemistry, and urinalysis were similar for both COPAXONE and placebo groups in blinded clinical trials. In controlled trials one patient discontinued treatment due to thrombocytopenia ($16 \times 10^9/L$), which resolved after discontinuation of treatment.

Data on adverse reactions occurring in the controlled clinical trials were analyzed to evaluate differences based on sex. No clinically significant differences were identified. Ninety-six percent of patients in these clinical trials were Caucasian. The majority of patients treated with COPAXONE were between the ages of 18 and 45. Consequently, data are inadequate to perform an analysis of the adverse reaction incidence related to clinically relevant age subgroups.

Other Adverse Reactions

In the paragraphs that follow, the frequencies of less commonly reported adverse clinical reactions are presented. Because the reports include reactions observed in open and uncontrolled premarketing studies (n= 979), the role of COPAXONE in their causation cannot be reliably determined. Furthermore, variability associated with adverse reaction reporting, the terminology used to describe adverse reactions, etc., limit the value of the quantitative frequency estimates provided. Reaction frequencies are calculated as the number of patients who used COPAXONE and reported a reaction divided by the total number of patients exposed to COPAXONE. All reported reactions are included except those already listed in the previous table, those too general to be informative, and those not reasonably associated with the use of the drug. Reactions are further classified within body system categories and enumerated in order of decreasing frequency using the following definitions: *Frequent* adverse reactions are defined as those occurring in at least 1/100 patients and *infrequent* adverse reactions are those occurring in 1/100 to 1/1,000 patients.

Body as a Whole:

Frequent: Abscess

Infrequent: Injection site hematoma, injection site fibrosis, moon face, cellulitis, generalized edema, hernia, injection site abscess, serum sickness, suicide attempt, injection site hypertrophy, injection site melanosis, lipoma, and photosensitivity reaction.

Cardiovascular:

Frequent: Hypertension.

Infrequent: Hypotension, midsystolic click, systolic murmur, atrial fibrillation, bradycardia, fourth heart sound, postural hypotension, and varicose veins.

Digestive:

Infrequent: Dry mouth, stomatitis, burning sensation on tongue, cholecystitis, colitis, esophageal ulcer, esophagitis, gastrointestinal carcinoma, gum hemorrhage, hepatomegaly, increased appetite, melena, mouth ulceration, pancreas disorder, pancreatitis, rectal hemorrhage, tenesmus, tongue discoloration, and duodenal ulcer.

Endocrine:

Infrequent: Goiter, hyperthyroidism, and hypothyroidism.

Gastrointestinal:

Frequent: Bowel urgency, oral moniliasis, salivary gland enlargement, tooth caries, and ulcerative stomatitis.

Hemic and Lymphatic:

Infrequent: Leukopenia, anemia, cyanosis, eosinophilia, hematemesis, lymphedema, pancytopenia, and splenomegaly.

Metabolic and Nutritional:

Infrequent: Weight loss, alcohol intolerance, Cushing's syndrome, gout, abnormal healing, and xanthoma.

Musculoskeletal:

Infrequent: Arthritis, muscle atrophy, bone pain, bursitis, kidney pain, muscle disorder, myopathy, osteomyelitis, tendon pain, and tenosynovitis.

Nervous:

Frequent: Abnormal dreams, emotional lability, and stupor.

Infrequent: Aphasia, ataxia, convulsion, circumoral paresthesia, depersonalization, hallucinations, hostility, hypokinesia, coma, concentration disorder, facial paralysis, decreased libido, manic reaction, memory impairment, myoclonus, neuralgia, paranoid reaction, paraplegia, psychotic depression, and transient stupor.

Respiratory:

Frequent: Hyperventilation and hay fever.

Infrequent: Asthma, pneumonia, epistaxis, hypoventilation, and voice alteration.

Skin and Appendages:

Frequent: Eczema, herpes zoster, pustular rash, skin atrophy, and warts.

Infrequent: Dry skin, skin hypertrophy, dermatitis, furunculosis, psoriasis, angioedema, contact dermatitis, erythema nodosum, fungal dermatitis, maculopapular rash, pigmentation, benign skin neoplasm, skin carcinoma, skin striae, and vesiculobullous rash.

Special Senses:

Frequent: Visual field defect.

Infrequent: Dry eyes, otitis externa, ptosis, cataract, corneal ulcer, mydriasis, optic neuritis, photophobia, and taste loss.

Urogenital:

Frequent: Amenorrhea, hematuria, impotence, menorrhagia, suspicious papaincolaou smear, urinary frequency, and vaginal hemorrhage.

Infrequent: Vaginitis, flank pain (kidney), abortion, breast engorgement, breast enlargement, carcinoma *in situ* cervix, fibrocystic breast, kidney calculus, nocturia, ovarian cyst, priapism, pyelonephritis, abnormal sexual function, and urethritis.

6.2 Postmarketing Experience

Reports of adverse events occurring under treatment with COPAXONE not mentioned above that have been received since market introduction and may or may not have causal relationship to COPAXONE are listed below. Because these events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Body as a Whole: sepsis; SLE syndrome; hydrocephalus; enlarged abdomen; injection site hypersensitivity; allergic reaction; anaphylactoid reaction

Cardiovascular System: thrombosis; peripheral vascular disease; pericardial effusion; myocardial infarct; deep thrombophlebitis; coronary occlusion; congestive heart failure; cardiomyopathy; cardiomegaly; arrhythmia; angina pectoris

Digestive System: tongue edema; stomach ulcer; hemorrhage; liver function abnormality; liver damage; hepatitis; eructation; cirrhosis of the liver; cholelithiasis

Hemic and Lymphatic System: thrombocytopenia; lymphoma-like reaction; acute leukemia

Metabolic and Nutritional Disorders: hypercholesterolemia

Musculoskeletal System: rheumatoid arthritis; generalized spasm

Nervous System: myelitis; meningitis; CNS neoplasm; cerebrovascular accident; brain edema; abnormal dreams; aphasia; convulsion; neuralgia

Respiratory System: pulmonary embolus; pleural effusion; carcinoma of lung; hay fever

Special Senses: glaucoma; blindness; visual field defect

Urogenital System: urogenital neoplasm; urine abnormality; ovarian carcinoma; nephrosis; kidney failure; breast carcinoma; bladder carcinoma; urinary frequency

7 DRUG INTERACTIONS

Interactions between COPAXONE and other drugs have not been fully evaluated. Results from existing clinical trials do not suggest any significant interactions of COPAXONE with therapies commonly used in MS patients, including the concurrent use of corticosteroids for up to 28 days. COPAXONE has not been formally evaluated in combination with interferon beta.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category B.

Administration of glatiramer acetate by subcutaneous injection to pregnant rats and rabbits resulted in no adverse effects on offspring development. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, COPAXONE should be used during pregnancy only if clearly needed.

In rats or rabbits receiving glatiramer acetate by subcutaneous injection during the period of organogenesis, no adverse effects on embryo-fetal development were observed at doses up to 37.5 mg/kg/day (18 and 36 times, respectively, the therapeutic human dose of 20 mg/day on a mg/m² basis). In rats receiving subcutaneous glatiramer acetate at doses of up to 36 mg/kg from day 15 of pregnancy throughout lactation, no significant effects on delivery or on offspring growth and development were observed.

8.2 Labor and Delivery

The effects of COPAXONE on labor and delivery in pregnant women are unknown.

8.3 Nursing Mothers

It is not known if glatiramer acetate is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when COPAXONE is administered to a nursing woman.

8.4 Pediatric Use

The safety and effectiveness of COPAXONE have not been established in patients under 18 years of age.

8.5 Geriatric Use

COPAXONE has not been studied in elderly patients.

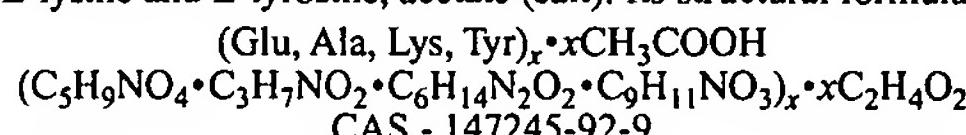
8.6 Use in Patients with Impaired Renal Function

The pharmacokinetics of glatiramer acetate in patients with impaired renal function have not been determined.

11 DESCRIPTION

COPAXONE is the brand name for glatiramer acetate (formerly known as copolymer-1). Glatiramer acetate, the active ingredient of COPAXONE, consists of the acetate salts of synthetic polypeptides, containing four naturally occurring amino acids: L-glutamic acid, L-alanine, L-tyrosine, and L-lysine with an average molar fraction of 0.141, 0.427, 0.095, and 0.338, respectively. The average molecular weight of glatiramer acetate is 5,000 – 9,000 daltons. Glatiramer acetate is identified by specific antibodies.

Chemically, glatiramer acetate is designated L-glutamic acid polymer with L-alanine, L-lysine and L-tyrosine, acetate (salt). Its structural formula is:



COPAXONE is a clear, colorless to slightly yellow, sterile, nonpyrogenic solution for subcutaneous injection. Each 1 mL of solution contains 20 mg of glatiramer acetate and 40 mg of mannitol. The pH range of the solution is approximately 5.5 to 7.0. The biological activity of COPAXONE is determined by its ability to block the induction of experimental autoimmune encephalomyelitis (EAE) in mice.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The mechanism(s) by which glatiramer acetate exerts its effects in patients with MS are not fully understood. However, glatiramer acetate is thought to act by modifying immune processes that are believed to be responsible for the pathogenesis of MS. This hypothesis is supported by findings of studies that have been carried out to explore the pathogenesis of experimental autoimmune encephalomyelitis, a condition induced in animals through immunization against central nervous system derived material containing myelin and often used as an experimental animal model of MS. Studies in animals and *in vitro* systems suggest that upon its administration, glatiramer acetate-specific suppressor T-cells are induced and activated in the periphery.

Because glatiramer acetate can modify immune functions, concerns exist about its potential to alter naturally occurring immune responses. There is no evidence that glatiramer acetate does this, but this has not been systematically evaluated [see Warnings and Precautions (5.4)].

12.2 Pharmacokinetics

Results obtained in pharmacokinetic studies performed in humans (healthy volunteers) and animals support that a substantial fraction of the therapeutic dose delivered to patients subcutaneously is hydrolyzed locally. Larger fragments of glatiramer acetate can be recognized by glatiramer acetate-reactive antibodies. Some fraction of the injected material, either intact or partially hydrolyzed, is presumed to enter the lymphatic circulation, enabling it to reach regional lymph nodes, and some may enter the systemic circulation intact.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

In a 2-year carcinogenicity study, mice were administered up to 60 mg/kg/day glatiramer acetate by subcutaneous injection (up to 15 times the human therapeutic dose of 20 mg/day on a mg/m² basis). No increase in systemic neoplasms was observed. In males receiving the 60-mg/kg/day dose, there was an increased incidence of fibrosarcomas at the injection sites. These sarcomas were associated with skin damage precipitated by repetitive injections of an irritant over a limited skin area.

In a 2-year carcinogenicity study, rats were administered up to 30 mg/kg/day glatiramer acetate by subcutaneous injection (up to 15 times the human therapeutic dose on a mg/m² basis). No increase in neoplasms was observed.

Glatiramer acetate was not mutagenic in *in vitro* (Ames test, mouse lymphoma tk) assays. Glatiramer acetate was clastogenic in two separate *in vitro* chromosomal aberration assays in cultured human lymphocytes but not clastogenic in an *in vivo* mouse bone marrow micronucleus assay.

When glatiramer acetate was administered by subcutaneous injection prior to and during mating (males and females) and throughout gestation and lactation (females) at doses up to 36 mg/kg/day (18 times the human therapeutic dose on a mg/m² basis) no adverse effects were observed on reproductive or developmental parameters.

14 CLINICAL STUDIES

14.1 Relapsing-Remitting Multiple Sclerosis (RRMS)

Evidence supporting the effectiveness of COPAXONE in decreasing the frequency of relapses derives from 3 placebo-controlled trials, all of which used a COPAXONE dose of 20 mg/day.

Study 1 was performed at a single center. Fifty patients were enrolled and randomized to receive daily doses of either COPAXONE, 20 mg subcutaneously, or placebo (COPAXONE: n=25; placebo: n=25). Patients were diagnosed with RRMS by standard criteria, and had had at least 2 exacerbations during the 2 years immediately preceding enrollment. Patients were ambulatory, as evidenced by a score of no more than 6 on the Kurtzke Disability Scale Score (DSS), a standard scale rang-

ing from 0–Normal to 10–Death due to MS. A score of 6 is defined as one at which a patient is still ambulatory with assistance; a score of 7 means the patient must use a wheelchair.

Patients were examined every 3 months for 2 years, as well as within several days of a presumed exacerbation. To confirm an exacerbation, a blinded neurologist had to document objective neurologic signs, as well as document the existence of other criteria (e.g., the persistence of the neurological signs for at least 48 hours).

The protocol-specified primary outcome measure was the proportion of patients in each treatment group who remained exacerbation free for the 2 years of the trial, but two other important outcomes were also specified as endpoints: the frequency of attacks during the trial, and the change in the number of attacks compared with the number which occurred during the previous 2 years.

Table 2 presents the values of the three outcomes described above, as well as several protocol-specified secondary measures. These values are based on the intent-to-treat population (i.e., all patients who received at least 1 dose of treatment and who had at least 1 on-treatment assessment):

Table 2: Study 1 Efficacy Results

| | COPAXONE (N=25) | Placebo (N=25) | P-Value |
|--|--------------------|-------------------|---------|
| % Relapse-Free Patients | 14/25 (56%) | 7/25 (28%) | 0.085 |
| Mean Relapse Frequency | 0.6/2 years | 2.4/2 years | 0.005 |
| Reduction in Relapse Rate Compared to Prestudy | 3.2 | 1.6 | 0.025 |
| Median Time to First Relapse (days) | >700 | 150 | 0.03 |
| % of Progression-Free* Patients | 20/25 (80%) | 13/25 (52%) | 0.07 |

*Progression was defined as an increase of at least 1 point on the DSS, persisting for at least 3 consecutive months.

Study 2 was a multicenter trial of similar design which was performed in 11 US centers. A total of 251 patients (COPAXONE: n=125; placebo: n=126) were enrolled. The primary outcome measure was the Mean 2-Year Relapse Rate. Table 3 presents the values of this outcome for the intent-to-treat population, as well as several secondary measures:

Table 3: Study 2 Efficacy Results

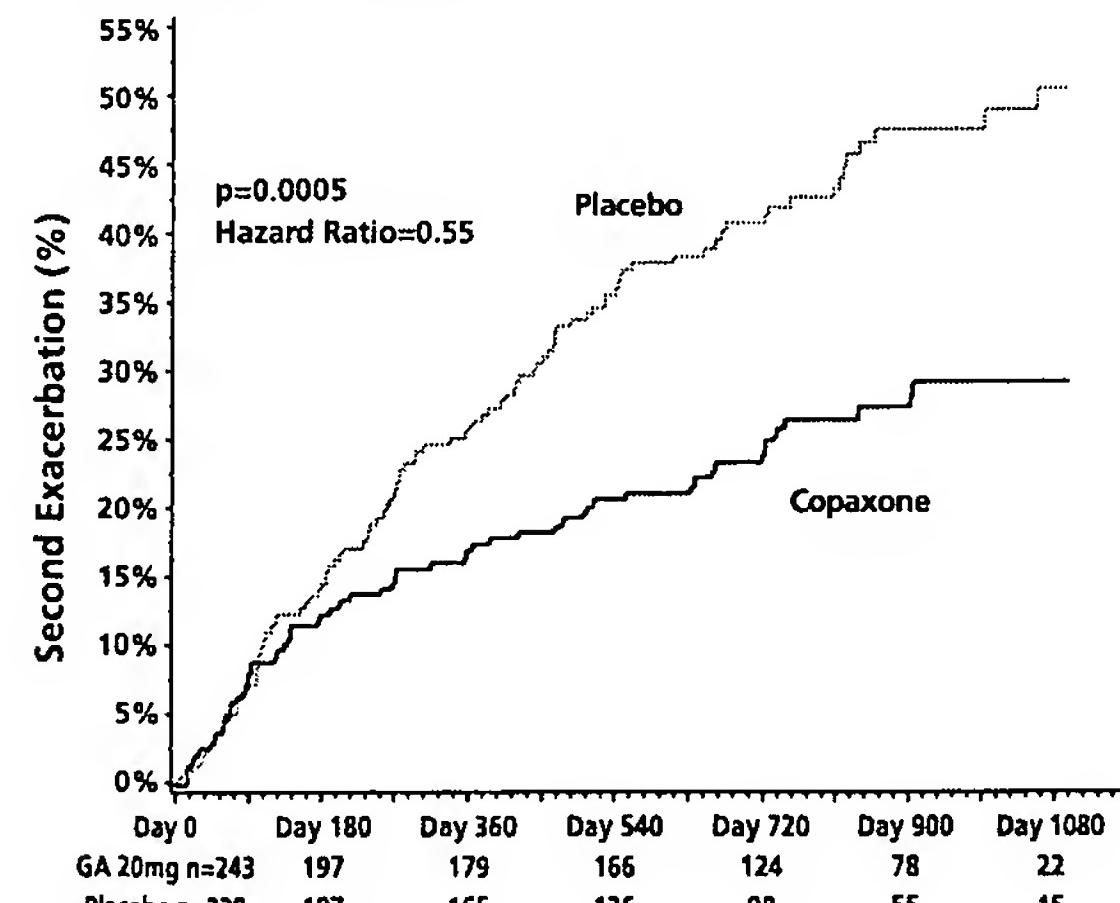
| | COPAXONE (N=125) | Placebo (N=126) | P-Value |
|-------------------------------------|---------------------|--------------------|---------|
| Mean No. of Relapses | 1.19/2 years | 1.68/2 years | 0.055 |
| % Relapse-Free Patients | 42/125 (34%) | 34/126 (27%) | 0.25 |
| Median Time to First Relapse (days) | 287 | 198 | 0.23 |
| % of Progression-Free Patients | 98/125 (78%) | 95/126 (75%) | 0.48 |
| Mean Change in DSS | -0.05 | +0.21 | 0.023 |

In both studies, COPAXONE exhibited a clear beneficial effect on relapse rate, and it is based on this evidence that COPAXONE is considered effective.

In Study 3, 481 patients who had recently (within 90 days) experienced an isolated demyelinating event and who had lesions typical of multiple sclerosis on brain MRI were randomized to receive either COPAXONE 20 mg/day (n=243) or placebo (n=238). The primary outcome measure was time to development of a second exacerbation. Patients were followed for up to three years or until they reached the primary endpoint. Secondary outcomes were brain MRI measures, including number of new T2 lesions and T2 lesion volume.

Time to development of a second exacerbation was significantly delayed in patients treated with COPAXONE compared to placebo (Hazard Ratio = 0.55; 95% confidence interval 0.40 to 0.77; Figure 1). The Kaplan-Meier estimates of the percentage of patients developing a relapse within 36 months were 42.9% in the placebo group and 24.7% in the COPAXONE group.

Figure 1: Time to Second Exacerbation



Patients treated with COPAXONE demonstrated fewer new T2 lesions at the last observation (rate ratio 0.41; confidence interval 0.28 to 0.59; $p < 0.0001$). Additionally, baseline-adjusted T2 lesion volume at the last observation was lower for patients treated with COPAXONE (ratio of 0.89; confidence interval 0.84 to 0.94; $p = 0.0001$).

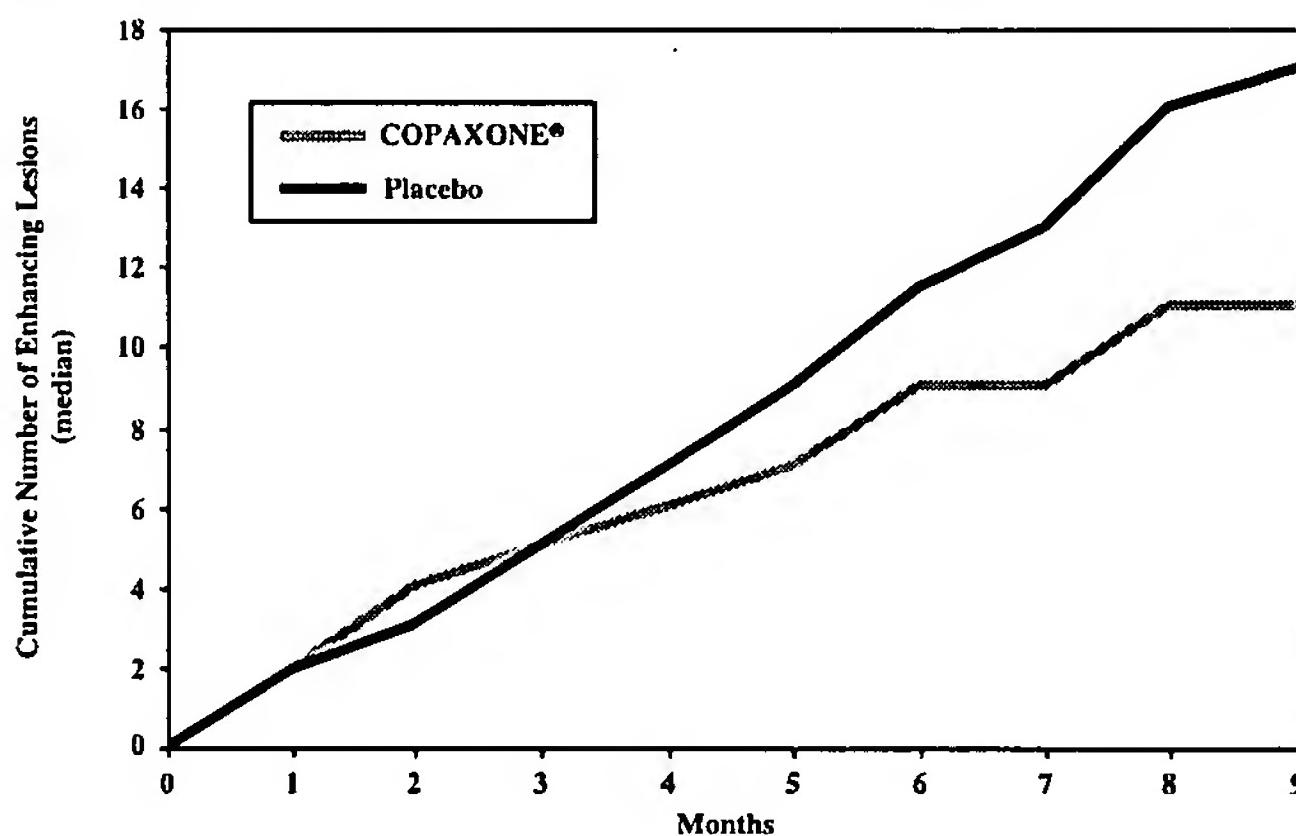
Study 4 was a multinational study in which MRI parameters were used both as primary and secondary endpoints. A total of 239 patients with RRMS (COPAXONE: n=119; and placebo: n=120) were randomized. Inclusion criteria were similar to those in the second study with the additional criterion that patients had to have at least one Gd-enhancing lesion on the screening MRI. The patients were treated in a double-blind manner for nine months, during which they underwent monthly MRI scanning. The primary endpoint for the double-blind phase was the total cumulative number of T1 Gd-enhancing lesions over the nine months. Table 4 summarizes the results for the primary outcome measure monitored during the trial for the intent-to-treat cohort.

Table 4: Study 4 MRI Results

| | COPAXONE (N=119) | Placebo (N=120) | P-Value |
|---|---------------------|--------------------|---------|
| Medians of the Cumulative Number of T1 Gd-Enhancing Lesions | 11 | 17 | 0.0030 |

Figure 2 displays the results of the primary outcome on a monthly basis.

Figure 2: Median Cumulative Number of Gd-Enhancing Lesions



16 HOW SUPPLIED/STORAGE AND HANDLING

COPAXONE is supplied as a single-use prefilled syringe containing 1 mL of a clear, colorless to slightly yellow, sterile, nonpyrogenic solution containing 20 mg of glatiramer acetate and 40 mg of mannitol in cartons of 30 single-use prefilled syringes with 33 alcohol preps (NDC 68546-317-30).

The recommended storage condition for the COPAXONE is refrigeration (2°C to 8°C / 36°F to 46°F). However, excursions from recommended storage conditions (15°C to 30°C / 59°F to 86°F) for up to one month have been shown to have no adverse impact on the product. Exposure to higher temperatures or intense light should be avoided. COPAXONE should not be frozen. If a COPAXONE syringe freezes, it should be discarded.

COPAXONE contains no preservative. Do not use if the solution contains any particulate matter.

17 PATIENT COUNSELING INFORMATION

[See FDA-Approved Patient Labeling (17.7)]

17.1 Pregnancy

Instruct patients that if they are pregnant or plan to become pregnant while taking COPAXONE they should inform their physician.

17.2 Immediate Post-Injection Reaction

Advise patients that COPAXONE may cause various symptoms after injection, include flushing, chest pain, palpitations, anxiety, dyspnea, constriction of the throat, and urticaria. These symptoms are generally transient and self-limited and do not require specific treatment. Inform patients that these symptoms may occur early or may have their onset several months after the initiation of treatment. A patient may experience one or several episodes of these symptoms.

17.3 Chest Pain

Advise patients that they may experience transient chest pain either as part of the Immediate Post-Injection Reaction or in isolation. Inform patients that the pain should be transient (usually only lasting a few minutes). Some patients may experience more than one such episode, usually beginning at least one month after the initiation of treatment. Patient should be advised to seek medical attention if they experience chest pain of unusual duration or intensity.

17.4 Lipoatrophy and Skin Necrosis at Injection Site

Advise patients that localized lipoatrophy, and rarely, injection site necrosis may occur at injections sites. Instruct patients to follow proper injection technique and to rotate injection areas and sites on a daily basis.

17.5 Instructions for Use

Instruct patients to read the COPAXONE Patient Information leaflet carefully. Caution patients to use aseptic technique. The first injection should be performed under the supervision of a health care professional. Instruct patients to rotate injection areas and sites on a daily basis. Caution patients against the reuse of needles or syringes. Instruct patients in safe disposal procedures.

17.6 Storage Conditions

Advise patients that the recommended storage condition for COPAXONE is refrigeration (36-46°F / 2-8°C), although COPAXONE can be stored at room temperature (59-86°F / 15-30°C) for up to one month. COPAXONE should not be exposed to higher temperatures or intense light.

17.7 FDA-Approved Patient Labeling

Read this information carefully before you use COPAXONE. Read the information you get when you refill your COPAXONE prescriptions because there may be new information. This information does not take the place of your doctor's advice. Ask your doctor or pharmacist if you do not understand some of this information or if you want to know more about this medicine.

What is COPAXONE?

COPAXONE (co-PAX-own) is a medicine you inject to treat Relapsing-Remitting Multiple Sclerosis. Although COPAXONE is not a cure; patients treated with COPAXONE have fewer relapses.

Who should not use COPAXONE?

- Do not use COPAXONE if you are allergic to glatiramer acetate or mannitol.

What are the possible side effects of COPAXONE?

- Call your doctor right away if you develop any of the following symptoms: hives, skin rash with irritation, dizziness, sweating, chest pain, trouble breathing, or severe pain at the injection site. Do not give yourself any more injections until your doctor tells you to begin again.
- The most common side effects of COPAXONE are redness, pain, swelling, itching, or a lump at the injection site. These reactions are usually mild and seldom require medical care.
- Some patients report a short-term reaction right after injecting COPAXONE. This reaction can involve flushing (feeling of warmth and/or redness), chest tightness or pain with heart palpitations, anxiety, and trouble breathing. These symptoms generally appear within minutes after an injection, last a few minutes, and then go away by themselves without further problems.
- A permanent depression under the skin at the injection site may occur, due to a local destruction of fat tissue.
- If symptoms become severe, call the emergency phone number in your area. Do not give yourself any more injections until your doctor tells you to begin again.

These are not all the possible side effects of COPAXONE. For a complete list, ask your doctor or pharmacist. Tell your doctor about any side effects you have while taking COPAXONE.

Information for pregnant and nursing women

- COPAXONE has not been studied in pregnant women. Talk to your doctor about the risks and benefits of COPAXONE if you are pregnant or planning a pregnancy.
- It is not known if COPAXONE passes into breastmilk. Talk to your baby's doctor about the risks and benefits of breastfeeding while using COPAXONE.

How should I use COPAXONE?

- The recommended dose of COPAXONE for the treatment of Relapsing-Remitting Multiple Sclerosis is 20 mg once a day injected subcutaneously (in the fatty layer under the skin).
- Look at the medicine in the prefilled syringe. If the medicine is cloudy or has particles in it, do not use it. Instead, call Shared Solutions® at 1-800-887-8100 for assistance.
- Have a friend or relative with you if you need help, especially when you first start giving yourself injections.
- Each prefilled syringe should be used for only one injection. Do not reuse the prefilled syringe. After use, throw it away properly.
- Do not change the dose or dosing schedule or stop taking the medicine without talking with your doctor.

How do I inject COPAXONE?

There are 3 basic steps for injecting COPAXONE prefilled syringes:

- Gather the materials.
- Choose the injection site.
- Give yourself the injection.

Step 1: Gather the materials

- First, place each of the items you will need on a clean, flat surface in a well-lit area:
 - 1 blister pack with COPAXONE Prefilled Syringe
Remove only 1 blister pack from the COPAXONE Prefilled Syringe carton.
Keep all unused syringes in the Prefilled Syringe carton and store them in the refrigerator.
 - Alcohol prep (wipe)
 - Dry cotton ball (not supplied)
- Let the blister pack with the syringe inside warm up to room temperature for 20 minutes.
- To prevent infection, wash and dry your hands. Do not touch your hair or skin after washing.

4. There may be small air bubbles in the syringe. To avoid loss of medicine when using COPAXONE prefilled syringes, do not expel (or do not attempt to expel) the air bubble from the syringe before injecting the medicine.

Step 2: Choose the injection site

- There are 7 possible injection areas on your body: arms, thighs, hips and lower stomach area (abdomen) (See Figure 1).

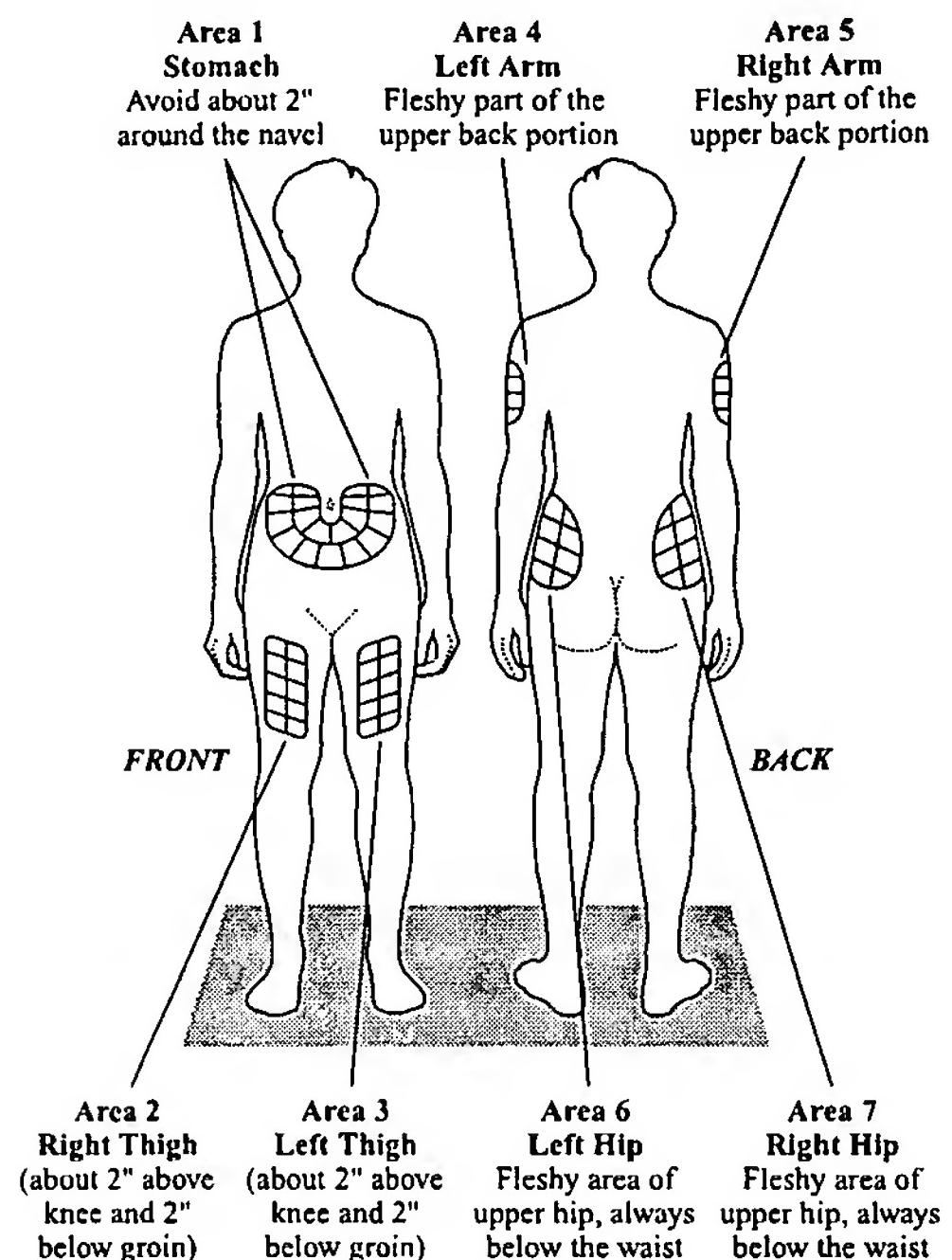


Figure 1

- Each day, pick a different injection area from one of the 7 areas. **Do not inject in the same area more than once a week.**
- Within each injection area there are multiple injection sites. Have a plan for rotating your injection sites. Keep a record of your injection sites, so you know where you have injected.
- There are some sites in your body that may be hard to reach for self-injection (like the back of your arm), and you may need help.
- Do not inject in sites where skin depression has occurred, because further injections in these sites may make the depression deeper.

Step 3: Give yourself the injection

1. Remove the syringe from its protective blister pack by peeling back the paper label. Before use, look at the liquid in the syringe. If it is cloudy or contains any particles, do not use it and call Shared Solutions® at 1-800-887-8100 for assistance. If the liquid is clear, place the syringe on the clean, flat surface.
2. Choose an injection site on your body. Clean the injection site with a new alcohol prep and let the site air dry to reduce stinging.
3. Pick up the syringe as you would a pencil. Remove the needle shield from the needle.
4. With your other hand, pinch about a 2-inch fold of skin between your thumb and index finger (See Figure 2).
5. Insert the needle at a 90-degree angle (straight in), resting the heel of your hand against your body. When the needle is all the way in release the fold of skin (See Figure 3).

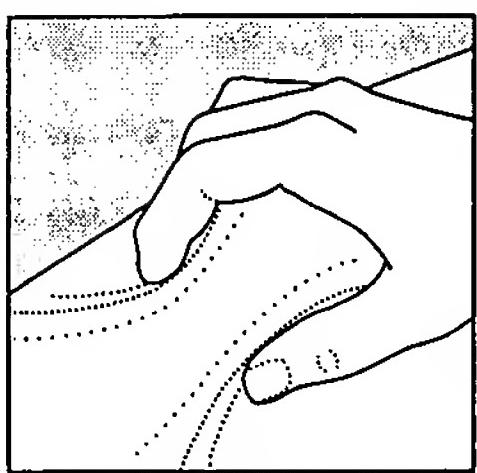


Figure 2

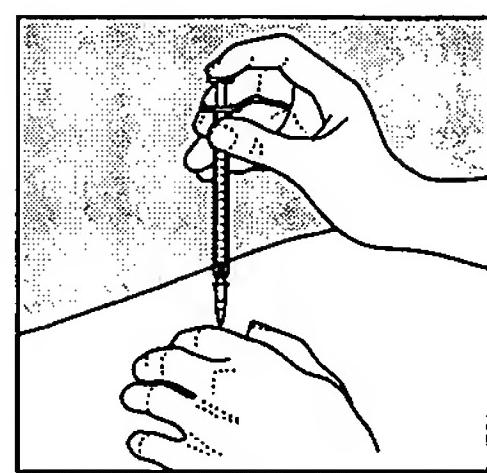


Figure 3

6. To inject the medicine, hold the syringe steady and push down the plunger.
7. When you have injected all of the medicine, pull the needle straight out.
8. Press a dry cotton ball on the injection site for a few seconds. **Do not rub the injection site.**
9. Throw away the syringe in a safe hard-walled plastic container.

What is the proper use and disposal of prefilled syringes?

Each prefilled syringe should be used for only 1 injection. Throw away all used prefilled syringes in a hard-walled plastic container, such as an empty liquid laundry detergent bottle. Keep the container closed tightly and out of the reach of children. When the container is full, check with your doctor, pharmacist, or nurse about proper disposal, as laws vary from state to state.

How should I store COPAXONE prefilled syringes?

Keep the COPAXONE prefilled syringe carton in the refrigerator, out of the reach of children.

The COPAXONE package should be refrigerated at 36-46°F (2-8°C). You can store it at room temperature, 59-86°F (15-30°C), for up to one month. Do not store COPAXONE at room temperature for longer than one month. **Do not freeze COPAXONE.** If a COPAXONE prefilled syringe freezes, throw it away in a proper container.

COPAXONE is light sensitive. Protect it from light when not injecting. Do not use the prefilled syringe if the solution contains particles or is cloudy.

General advice about prescription medicines

Medicines are sometimes prescribed for conditions that are not mentioned in patient information leaflets. Do not use COPAXONE for a condition for which it was not prescribed. Do not give COPAXONE to other people, even if they have the same condition you have. It may harm them.

This leaflet summarizes the most important information about COPAXONE. If you would like more information, talk with your doctor. You can ask your pharmacist or doctor for information about COPAXONE that is written for health professionals. Also, you can call Shared Solutions® for any questions about COPAXONE and its use. The phone number for Shared Solutions® is 1-800-887-8100.

U.S. Patent Nos. 5981589, 6054430, 6342476, 6362161, 6620847, 6939539, 7199098.



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